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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/292,217	04/15/1999	STEPHEN D. GILLIES	LEX-004	3227

21323 7590 01/02/2003

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/02/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/292,217	GILLIES, STEPHEN D.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002 and 22 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,12-18,20-24,27 and 31-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,12-18,20-24,27 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendments, filed 6/6/02, 8/22/02 and 11/1/02 (Paper Nos. 17, 19 and 20), are acknowledged.

Claims 3, 10, 11, 19, 25, 26, 28-30, 38 and 39 have been canceled.

Claims 1, 4, 5, 8, 9, 12-14, 17, 18, 20, 23, 24, 27, 31-33 and 36 have been amended.

Claims 1, 2, 4-9, 12-18, 20-24, 27 and 31-37 *are pending and being acted upon presently.*

2. The formal drawings filed 6/6/02 have been approved by the Draftsman.

3. This Office Action will be in response to Applicant's arguments, filed 6/6/02 (Paper No. 17). The rejections of record can be found in the previous Office Action (Paper Nos. 8, 10 and 15).

It is noted that New Grounds of Rejection are set forth herein.

4. Applicant's cancellation of claims 3, 10, 11, 19, 25, 26, 28-30, 38 and 39 has obviated the previous objections and rejections with respect to these claims.

5. The Non-statutory double patenting rejection set forth in Paper No. 8 is held in abeyance.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites the limitation "the cytokine" in the phrase "a CH3 domain interposed between the CH2 domain and the cytokine". There is insufficient antecedent basis for this limitation in the claim, because claim 36, from which claim 37 depends no longer generically recites "a cytokine".

It is suggested that Applicant amend claim 37 to recite -- interleukin-2 -- rather than "the cytokine".

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Applicant's amendment has obviated the previous rejection of:
claims 1-2 and 4-39 under 35 U.S.C. 103(a) as being unpatentable over Gilles et al. (WO 92/08495, IDS #BA), in view of O'Reilly et al. (Cell 88:277-285 1997, IDS # CV); and of
claims 1, 11, and 26 are rejected as being unpatentable over Gillies (WO 92/08495, IDS # BA) in view of O'Reilly et al. 1994 (Cell 79:315-328 1994, IDS # CU) or Brooks et al. (Cell 79:1157-1164 1994, IDS #CC) or Ingber et al. (Nature 348:555-557 1990, IDS# CM).

10. Claims 1, 2, 4-9, 12-18, 20-24, 27 and 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Proc. Natl. Acad. Sci. USA 1996; 93:2702-2707) in view of Carron et al. (U.S. Pat. No. 6,171,588).

Applicant's amendments, filed 6/6/02, 8/22/02 and 11/1/02 amends the claims to recite a method of inducing a cytocidal immune response against a solid tumor comprising administering an immunoconjugate that binds a target antigen associated with cancer on a target cell in a solid tumor and the cytokine IL-2, and an angiogenesis inhibitor that is an agent having binding affinity for $\alpha_v\beta_3$ integrin.

Becker et al. teach immunoconjugates comprising an antibody binding site specific for a target antigen associated with cancer and expressed on a target cell in solid tumor (i.e., either the EGF receptor or ganglioside GD_2 expressed by melanoma cells) and the cytokine IL-2 (see entire document, e.g., "Cell lines and Reagents" in Materials and Methods). Becker et al. teach the use of these immunoconjugates in inducing a cytocidal immune response against the solid tumor (see entire document).

Becker et al. teach that the immunoconjugate have the IL-2 cytokine attached to the carboxyl end of the antibody Cγ1 gene (see e.g. "Cell lines and Reagents" in Materials and Methods). Thus the immunoconjugates of Becker et al. comprise in an amino-terminal to carboxy-terminal direction the antibody binding site comprising the immunoglobulin variable region capable of binding the target antigen, the immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and immunoglobulin CH3 domain, and IL-2.

Becker et al. teach that IL-2 is one of the most potent antitumor cytokines known (e.g. page 2702, first column), and that immunoconjugates which combine a tumor specific antibody and IL-2 are more effective than administration of the antibody and IL-2 as separate compounds (e.g., page 2705, bridging paragraph and following paragraph).

Becker et al. do not teach compositions combining the immunoconjugate with an angiogenesis inhibitory having binding affinity for $\alpha_v\beta_3$ integrin, nor methods of using the combination of compositions.

Carron et al. teach compositions having binding affinity for $\alpha_v\beta_3$ integrin (see entire document). Carron et al. teach that compositions having binding affinity for $\alpha_v\beta_3$ integrin are useful in methods of inhibiting solid tumor growth (see entire document, but especially columns 3-5 and 19-20).

Carron et al. also teach that compositions having binding affinity for $\alpha_v\beta_3$ integrin may be combined with other pharmaceutical compositions or added to established anti-cancer chemotherapeutic or biotherapeutic regimens, including therapies involving the administration of IL-2 in the biological therapy of cancer (see especially column 13).

The ordinary artisan at the time the invention was made would have therefore found it obvious to combine the composition taught by Becker et al. with the composition taught by Carron et al. Further, the ordinary artisan would have found it obvious to use the composition resulting from the combination of the immunoconjugate of Becker et al. and the compositions having binding affinity for $\alpha_v\beta_3$ integrin of Carron et al. for use in an improved method of inducing a cytocidal immune response against a solid tumor. The timing of the administration of each component (either co-administration or sequential administration) would also have been obvious to the ordinary artisan at the time the invention was made and a matter of routine optimization.

Given the teachings of Carron et al. that the compositions having binding affinity for $\alpha_v\beta_3$ integrin should be combined with IL-2 based therapies of cancer, the ordinary artisan would clearly have been motivated to select the established IL-2 based therapy as taught by Becker et al. for combining with that of Carron et al. Further, given that both the immunoconjugate of Becker et al. and the compositions having binding affinity for $\alpha_v\beta_3$ integrin of Carron et al. are taught individually to be useful for the same purpose (therapy of cancer cells, including solid tumors) the ordinary artisan would have had a reasonable expectation the combination would induce a greater cytocidal immune response against the cancer cell, including cancer cells in a solid tumor, that was greater than a response induced by the immunoconjugate alone.

Applicant is again reminded that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 217 USPQ 1, 5 - 6 (Fed. Cir. 1983).

Applicant argues in the Remarks filed 6/6/02 that the instantly recited combination shows unexpected properties with respect to an effect on tumor cell growth, as evidenced by Lode et al. (Proc. Natl. Acad. Sci. USA 1999; 96:1591-1596).

Applicant's arguments, filed 6/6/02 have been fully considered, but have not been found convincing.

An expected beneficial result of a combination therapy is that the response induced is greater than that of either component. Thus the properties observed by Lode et al. are not unexpected.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claim allowed

12. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
December 30, 2002

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12/31/02